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Formulation development of methylprednisolone dispersible tablets using quality by design approach

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ABSTRACT

The objective of this study was to enhance the solubility of Methylprednisolone by choosing micronized form of drug and to enhance patient compliance by formulating it as dispersible tablets using quality by design (QbD) approach. Dispersible tablets of Methylprednisolone were developed by 2^3 factorial design. In this study independent variables were concentrations of MCC 102, CCS and Magnesium stearate and dependent variables were disintegration time, hardness and dissolution. The resulting data was fitted into Design Expert Software (Trial Version) and analyzed statistically using analysis of variance (ANOVA). The response surface plots were generated to determine the influence of concentration of MCC 102, CCS and magnesium stearate on responses. The tablets were prepared by direct compression method by choosing micronized form of drug and formulations were evaluated for the standard of dispersible tablets. Results showed that no significant drug-polymer interactions in FTIR studies. According to QbD suggestion the formulation O_1 (Desirability- 0.73) with MCC-38mg, CCS-3.5mg and magnesium stearate-2.5mg was formulated and evaluated. The disintegration time was found to be 69 seconds, hardness was found to be 64N and *in vitro* dissolution with in 30minutes. Optimized O_1 formulation was within the limits of standards of dispersible tablets with increased water solubility and better patient compliance. Stability study on optimized O_1 formulation showed that there is no significant changes during study period. Thus, O_1 formulation was found to be stable. The study indicates that formulation of Methylprednisolone dispersible tablets by using QbD approach is a promising formulation development method.

Keywords: Dispersible tablets, Methylprednisolone, Direct compression, Quality by Design and ANOVA.

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INTRODUCTION

The aim of the present work was to develop dispersible tablets of Methylprednisolone using quality risk management tool of the Quality by Design (QbD) approach. Various formulation variables involved in the development of dispersible tablets was identified and it was optimized for minimum risk level using design of experiments (DoE) tool for efficient reduction in the risk assessment. This reduces the risks involved in the development of dispersible tablets and yields a good quality product. The study describes elements of the QbD for Methylprednisolone dispersible tablets include: Defining quality target product profile, identifying critical quality attributes, establishing design space, control strategy. Risk assessment was done before applying DoE. This will reduce the risks involved in the development of dispersible tablets and yields a good quality product.[1]

A problem associated with Methylprednisolone is its poor dissolution characteristics with water solubility of about 120mcg/ml at 25˚C, which is a rate limiting step in the process of drug absorption.[2] For better patient compliance and increasing solubility micronisation and superdisintegrants addition turns out to be a best option. Thus dispersible tablets were formulated using direct compression technique by dry mixture of drug having a reduced particle size and to enhance disintegration superdisintegrants are added.[3] These agents are added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance.[4,5]

Dispersible tablets as defined in European Pharmacopoeia are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Typically a dispersible tablet is dispersed in about 5-15ml of water (e.g. in a tablespoonful or a glass of water) and the resulting dispersion is administered to the

patient. Dispersible tablets are required to disintegrate within 3min in water at 15-25° C. Also the dispersion produced from a dispersible tablet should pass through a sieve screen with a nominal mesh aperture of 710 microns.[6]

MATERIALS AND METHOD

Materials:

Methylprednisolone (Micronized), Lactose Monohydrate (DCL 11), Microcrystalline cellulose (Avicel PH 102), Croscarmellose sodium, Aspartame, Trusil orange, Colloidal silicon dioxide and Magnesium stearate.

Method:

All the materials were individually dispensed and weighed. The sifted Methylprednisolone, Lactose spray dried DCL11, Microcrystalline cellulose PH (102), Croscarmellose Sodium, Colloidal silicon dioxide, Trusil orange, and Aspartame was loaded into polybag and mixed well for 10minutes. To the above blend sifted Magnesium stearate was added and mixed for 2mins. By direct compression the final lubricated blend is compressed in a 16 station compression machine (Cadmach) with 8.00mm punch size, round standard concave punch with plain on both the surface.

Experimental Design

Particle size:

Micronized drug is chosen to increase solubility of drug. Particle size of micronized drug Methylprednisolone was found to be **1817nm** using particle analyzer (Malvern)**.**

Compatibility study of drug and excipients using Fourier transform infrared spectroscopy:

The FTIR spectra were recorded for pure drug and the physical mixture of drug and excipients at the scanning range of 4000-400 cm-1 using FTIR spectrophotometer (Shimadzu, Japan). FT-IR spectra of Methylprednisolone showed sharp characteristic peaks (Fig. 1). All the above characteristic peaks appeared in the spectra of physical mixture of drug (Fig. 2) and excipients at same wave number indicating no interaction between the drug and excipients.

Initial risk assessment of the Formulation variable for development of Methylprednisolone dispersible tablets:

A risk assessment of the drug substance was performed to evaluate the impact of CQA in product development. The relative risk assessment ranking system was used during development and it was summarized in Table 1. [7]

Quality Target Product Profile (QTPP) element analysis of drug product:

The QTPP is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."[8,9] The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product. The QTPP is a quantitative substitute for aspects of clinical safety and efficacy. QTPP of dispersible tablets includes the following elements:

Dosage Form	Pharmacokinetics	Impurities
Route of administration	Appearance	Content uniformity
Strength	Identity	Friability
Weight	Assay	Dissolution

Study of Critical Quality Attributes (CQA) of formulation and process:

It was stated that the ICH working definition of CQA was: "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure that the product meets its intended safety, efficacy, stability and performance."[10,11] CQA of dispersible tablets includes the following elements:

Identification	Weight variation	Disintegration	Assay
Appearance	Hardness	Dissolution	Product degradation

Optimization of the formulation of dispersible tablets using 2 level Factorial Design:

2^3 Factorial design (FD) formulations were developed with two center points. The Design Expert Software (Trial Version) suggested ten model formulations. Based on CQA to ensure safety, efficacy, stability and performance MCC, CCS and magnesium stearate were selected as independent variable and based on risk assessment study dissolution, disintegration time and hardness were selected as dependent variable for optimization study. Table 2 summarizes an account of all the actual values and levels of independent variables. All other formulation variables were kept in\variant throughout the study. The resulting data was fitted into Design Expert Software (Trial Version) and analyzed statistically using analysis of variance (ANOVA). The data was also subjected to response surface methodology to determine the influence of concentration of independent variable on responses.

Evaluation of Dispersible tablets:

To determine weight variation, twenty tablets were selected randomly from each formulation and were weighed individually using a digital balance (Essae). The individual weights were compared with the average weight for obtaining the weight variation.[12] Ten tablets from each formulation were selected randomly and their thickness was measured with a Vernier caliper (Mitutoyo). Hardness of the tablets was measured using a Hardness tester (Electrolab) and friability of a sample of twenty fast dissolving tablets was measured using a USP type-II Roche friabilator (Electrolab). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted,

reweighed and percentage weight loss (friability) was calculated. In vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of water and time required for complete dispersion was measured as shown in Fig. 3. Three tablets from each formulation were randomly selected and dispersion time was performed.[13] Uniformity of dispersion was determined by placing two tablets in 100ml of water and stirred gently until completely dispersed.[14] A smooth dispersion obtained should passes through sieve screen with nominal mesh aperture of 710µm (sieve no. 22). Dispersible tablets must disintegrate within 3min.

In vitro dissolution studies were performed in distilled water with volume of 900ml using USP apparatus Type –II (paddle) at temperature of 37±0.5°C.[15] The dissolution profiles of F1 to F10 formulations are depicted in Fig. 4.

Optimization of Methylprednisolone Dispersible Tablets Using 2 [3] Factorial Design:

Response 1 – Disintegration time:

Contour plot in Fig. 5 shows that Magnesium stearate in the level of 2.5-3.5mg and Croscarmellose sodium in the level 2.0-3.5mg will gives good result on disintegration time. 3D Response surface plot in Fig. 6 shows that disintegration time increase with increase in the concentration of magnesium stearate and disintegration time decreases by increasing the concentration of CCS. From ANOVA in Table 5 the Model F-value of 26.05 implies the **model is significant.** There is only a 0.40% chance that a "Model F-Value" this large could occur due to noise. In this case A, B, C, BC are significant model terms.

Response 2 – Hardness:

Contour plot in Fig. 7 shows that magnesium stearate in the level of 2.0-4.0mg and Microcrystalline cellulose in the level 37.5-41mg will gives good result on hardness. 3D Response surface plot in Fig. 8 shows that hardness increase with increase in the concentration of microcrystalline cellulose and hardness decreases by increasing the concentration of magnesium stearate. From ANOVA in Table 6 the Model F-value of 729.35 implies the **model is significant**. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, C, AC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Response 3 – *In vitro* Dissolution:

Contour plot in Fig. 9 shows that magnesium stearate in the level of 2.0-4.0mg and croscarmellose sodium in the level 2.5-3.5mg will gives good result on dissolution. 3D Response surface plot in Fig. 10 shows that dissolution increase with increase in the concentration of croscarmellose sodium and dissolution decreases by increasing the concentration of magnesium stearate. From ANOVA in Table 7 the Model F-value of 165.95 implies the **model is significant**. There is only a 0.07% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, C, AC, BC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Formulation and Evaluation of Optimized Formulation O_1:

From the results of optimization study it was found that MCC in the concentration 37- 41mg, CCS in concentration 2.5 – 3.5mg and magnesium stearate in concentration 2.5 – 3.5mg gives optimized product. So, Constrains are fixed as shown in Table 8 and according to QbD suggestion the formulation O_1 (Desirability- 0.73) with MCC-38mg, CCS-3.5mg and Magnesium stearate-2.5mg was formulated and evaluated for physical parameters and *in vitro* dissolution (Table 9).

Assay of optimized formulation O_1: (By HPLC)

Mobile phase: 475:475:70:35:30 (butyl chloride: water-saturated butyl chloride: THF: Methanol: glacial acetic acid); Wave length: 254nm. **Internal standard solution (ISS):** 20mg of prednisolone was weighed and dissolved in a 3% v/v solution of glacial acetic acid in chloroform (0.2mg/ml of prednisolone). **Reference solution** 20mg of drug was weighed and dissolved in 100ml of ISS (0.2mg/ml of drug). **Test solution:** A quantity of powdered tablet containing 10mg of drug was weighed and 50.0ml of ISS was added. 10µl of blank, reference solution and test solution was injected and the peak of drug was measured.[16]

Related substances of optimized formulation O_1: (By HPLC)

Mobile phase: 19:40:10 (water: THF: dimethylsulfoxide); Flow rate: 1.0ml/minute; Wave length: 254nm; **Solvent mixture**: 72:25:3 (water: THF: GAA) **Test solution**: A quantity of the powdered tablets containing 25mg of the drug was extracted and 25ml of solvent mixture was added. **Reference solution**: 0.001%w/v of Methylprednisolone in solvent mixture was reference solution. Reference solution and test solution was injected and impurities are measured.[16]

Release Kinetics of Optimized formulation O_1:

The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model like, zero-order, first-order, higuchi, korsmeyer–peppas and hixon.R^2 value of Higuchi model is very near to one for all most all the formulations than the R^2 values of other kinetic models. Thus, it can be said that the drug release follows higuchi release mechanism. Further the n value of Korsmeyer–Peppas model for the optimized formulation was 1.095. Therefore, the most probable mechanism of release was Super case II transport.

Stability study for optimized formulation O_1:

In the present study, stability studies were carried out on optimized formulation under accelerated study at 40±2ºC and RH 75% condition for three months. The tablets were withdrawn at 1st and 3rd month and analyzed for physical characterization and drug release as shown in Table 10.

RESULTS AND DISCUSSION

As the material was free flowing (angle of repose value <30" and Carrs index <15%), tablets obtained were of uniform weight (due to uniform die fill). All the formulated (F1 to F10) tablets passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight. The prepared formulation complies with the weight variation test. The maximum thickness of the formulation was found to be 4.0mm. The minimum thickness of the formulation was found to be 3.2mm. The hardness of the tablet was found to be 44 – 110N. The maximum friability of the formulation was found to be 0.96%. The minimum friability of the formulation was found to be 0.85%. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. In vitro Disintegration time was found to be in the range 47 – 147 sec. All the formulations passes the uniformity of dispersion test. Dispersion time was found to be in the range 25 – 46sec for all the formulation. Among all the formulations F5, F6, F7 and F8 shows 100%

drug release within 30minutes and all the formulations complies the *in vitro* dissolution test for dispersible tablets.

Based on CQA to ensure that the product meets its intended safety, efficacy, stability and performance microcrystalline cellulose, croscarmellose sodium and magnesium stearate were selected as independent variable and based on risk assessment study dissolution, disintegration time and hardness were selected as dependent variable for optimization study. From the results of optimization study it was found that MCC in the concentration 37- 41mg, CCS in concentration 2.5 – 3.5mg and magnesium stearate in concentration 2.5 – 3.5mg gives optimized product. So, constrains are fixed from results of study.

According to QbD suggestion the formulation O_1 (Desirability- 0.73) with MCC-38mg, CCS-3.5mg and magnesium stearate-2.5mg was formulated and evaluated. The disintegration time was found to be 69 seconds, hardness was found to be 64N and *in vitro* dissolution with in 30minutes. Assay for optimized O_1 formulation was found to be 102.25% and related substances of known and unknown impurities was found to be 0.04% and 0.02% respectively. Thus optimized O_1 formulation was within the limits of standards of dispersible tablets with increased water solubility and better patient compliance.

Short-term stability studies of the above formulation indicated that there are no signicant changes in physical characterization and drug release at the end of 3 month period ($P<0.05$). Thus O_1 formulation was found to be stable.

Thus formulation of Methylprednisolone dispersible tablets by selecting micronized form of drug for increasing water solubility will reduces the problem associated with selected drug. Present scenario of Methylprednisolone dispersible tablets will finds a greater advantage due to its flexible design, better patient compliance, masking bitter taste of drug, combines the advantages of conventional dosage form, cost effectiveness and use of QbD approach for minimizing the risks involved in the development of dispersible tablets will yields a good quality product when compared to other coventional forms. Ensures better design of products with fewer problems in manufacturing. It is a cost effective method to develop generic drug production. The product can be consistently produced without batch to batch variations.

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DECLARATION OF INTEREST

The authors of the manuscripts report no declaration of interest. The authors are alone responsible for the content and writing of the paper.

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Table 1: Initial risk assessment of the Formulation variable for development of Methylprednisolone dispersible tablets.

Drug product CQA	Identification of risk			
	Lactose DCL11	MCC 102	CCS	Magnesium stearate
Assay	Low	Low	Low	Low
RS	Low	Low	Low	Medium
Hardness	Low	High	Medium	High
Dispersion test	Low	Medium	High	High
Dissolution	Low	Medium	High	High
Disintegration	Low	Medium	High	High

Table 2: Optimization design summary

Design Summary			
Study Type	Factorial	Design Model	3FI
Initial Design	2 Level Factorial	Runs	10
Center Points	2	Blocks	No Blocks

Factor	Name	Units	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	MCC 102	mg	35	45	-1	1	40	4.472135955
B	CCS	mg	2	4	-1	1	3	0.894427191
C	mg stearate	mg	2	4	-1	1	3	0.894427191

Table 3: Composition of Methylprednisolone Dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	mg/tab									
API	16.00	16.00	16.00	16.00	16.00	16.00	16.00	16.00	16.00	16.00
Lactose (DCL 11)	138.5	128.5	136.5	126.5	131.5	131.5	136.5	126.5	134.5	124.5
MCC (Avicel 102)	35.00	45.00	35.00	45.00	40.00	40.00	35.00	45.00	35.00	45.00
CCS	2.00	2.00	2.00	2.00	3.00	3.00	4.00	4.00	4.00	4.00
Colloidal silicon dioxide	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Trusil Orange	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Aspartame	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	2.00	2.00	4.00	4.00	3.00	3.00	2.00	2.00	4.00	4.00
Tablet weight	200.00mg									

Table 4: Evaluation of physical properties of tablet formulations

Code	Weight variation* (mg)	Hardness(N)*	Thickness (mm)	Friability (%)	Uniformity of dispersion*	Dispersion time* (sec)	Dt time** (sec)
F1	200.12±1.2	55±5	3.3±0.02	0.86±0.01	Passes	32±09	62±06
F2	200.05±0.9	110±6	3.9±0.03	0.91±0.02	Passes	39±12	87±09
F3	200.12±1.6	44±7	3.5±0.02	0.89±0.02	Passes	43±16	127±10
F4	199.59±0.8	61±6	3.9±0.01	0.85±0.01	Passes	46±15	147±09
F5	200.21±0.5	75±8	4.0±0.03	0.93±0.02	Passes	26±18	47±06
F6	199.56±1.3	76±5	3.6±0.04	0.96±0.03	Passes	25±06	48±05
F7	200.36±1.6	52±3	3.7±0.03	0.87±0.01	Passes	30±10	57±08
F8	199.58±0.7	110±8	3.2±0.01	0.86±0.01	Passes	37±09	83±10
F9	200.63±0.6	47±6	3.6±0.02	0.96±0.02	Passes	32±07	69±07
F10	199.25±1.2	63±5	3.5±0.03	0.82±0.03	Passes	32±06	66±06

*Average of 3 determinations ±standard deviation.

Table 5: ANOVA for Disintegration time

Source	Sum of squares	df	Mean square	F value	p-value	
Model	7228.5	4	1807.125	26.04865	0.0040	**Significant**
A-MCC 102	578	1	578	8.331532	0.0447	
B-CCS	2738	1	2738	39.46667	0.0033	
C-mg stearate	1800	1	1800	25.94595	0.0070	
BC	2112.5	1	2112.5	30.45045	0.0053	
Curvature	2528.1	1	2528.1	36.44108	0.0038	Significant
Residual	277.5	4	69.375			
Lack of Fit	277	3	92.33333	184.6667	0.0540	
Pure Error	0.5	1	0.5			
Cor Total	10034.1	9				

Table 6: ANOVA for Hardness

Source	Sum of squares	df	Mean square	F value	p-value	
Model	5033	3	1678	729.34783	**< 0.0001**	**significant**
A-MCC 102	2665	1	2665	1158.4783	< 0.0001	
C-mg stearate	1568	1	1568	681.73913	< 0.0001	
AC	800	1	800	347.82609	< 0.0001	
Curvature	96.1	1	96.1	41.782609	0.0013	**significant**
Residual	11.5	5	2.3			
Lack of Fit	11	4	2.75	5.5	0.3082	
Pure Error	0.5	1	0.5			
Cor Total	5140	9				

Table 7: ANOVA for *in vitro* dissolution

Source	Sum of squares	df	Mean square	F value	p-value	
Model	1728.625	5	345.725	165.948	**0.0007**	**significant**
A-MCC 102	105.125	1	105.125	50.46	0.0057	
B-CCS	1431.125	1	1431.125	686.94	0.0001	
C-mg stearate	120.125	1	120.125	57.66	0.0047	
AC	36.125	1	36.125	17.34	0.0252	
BC	36.125	1	36.125	17.34	0.0252	
Curvature	511.225	1	511.225	245.388	0.0006	**significant**
Residual	6.25	3	2.083333333			
Lack of Fit	6.25	2	3.125			
Pure Error	0	1	0			
Cor Total	2246.1	9				

Table 8: Optimization Constraints

Name	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
MCC 102	is in range	38	41	1	1	3
CCS	is in range	2.5	3.5	1	1	3
Mg stearate	is in range	2.5	3.5	1	1	1
Disintegration time	minimize	47	147	1	1	5
Hardness	is in range	44	110	1	1	1
Dissolution	maximize	59	99	1	1	5

Table 9: Composition and physical parameters evaluation of Optimized O_1 formulation

Ingredients	Concentration (mg)
Methylprednisolone	16
Lactose	133.5
MCC	**38**
CCS	**3.5**
Colloidal SiO_2	3.0
Trusil Orange	1.0
Aspartame	2.5
Mg stearate	**2.5**
Tablet weight	200

Test	Result
Weight variation (mg)	200.17± 0.13
Hardness (N)	64±1
Thickness (mm)	3.5 ± 0.3
Friability (%)	0.83± 0.03
Disintegration time (sec)	69±2
Dissolution (%DR)	100% around 30 minutes.
Dispersion test	Complies

Table 10: Stability Compilation for Methylprednisolone dispersible tablets

Test Parameters	Acceptance criteria	Initial results	Condition - 40 ±20ºC & 75±5% RH	
			1st month	3rd month
Appearance*	White colored round shaped tablets, plain on both sides.	Complies	Complies	Complies
Average weight* (mg)	200mg ± 7.5% (185.00mg – 215.00mg)	200.17± 0.13	200.12± 0.19	199.78± 0.21
Hardness* (N)	NLT 30N	64±1	67±2	66±2
Disintegration Time* (Sec)	NMT 3minutes	69±2	68±3	68±3
Fineness of Dispersion*	A smooth dispersion is obtained which passes through a sieve screen with a nominal mesh aperture of 710µ	Complies	Complies	Complies
Dissolution*	NLT 70% of label claim	100%	100%	100%

***Average of 3 determinations** **±standard deviation.**

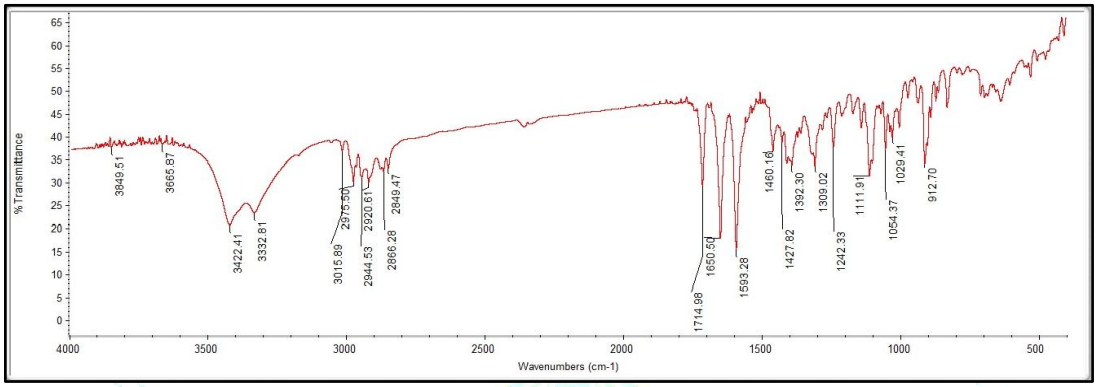

Figure 1: IR spectra of Methylprednisolone

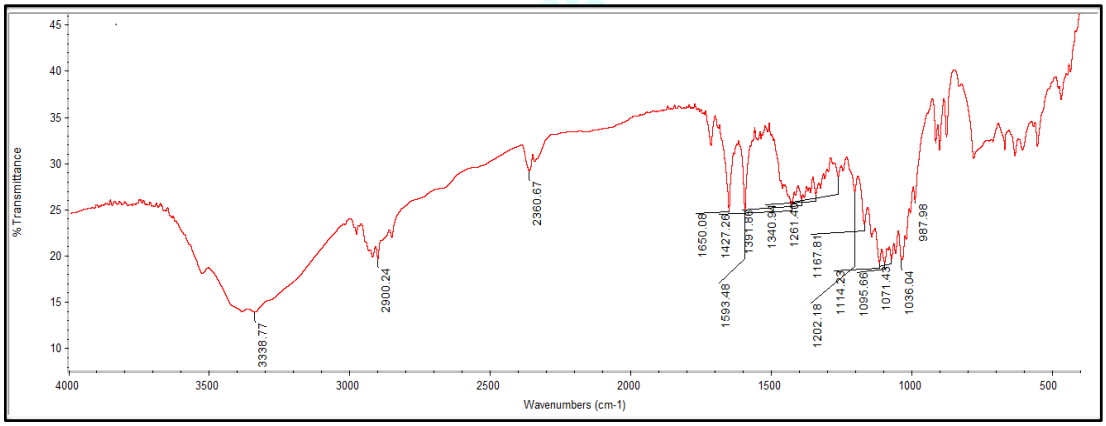

Figure 2: IR spectra of Physical mixture

Figure 3: Dispersion test for Methylprednisolone dispersible tablets

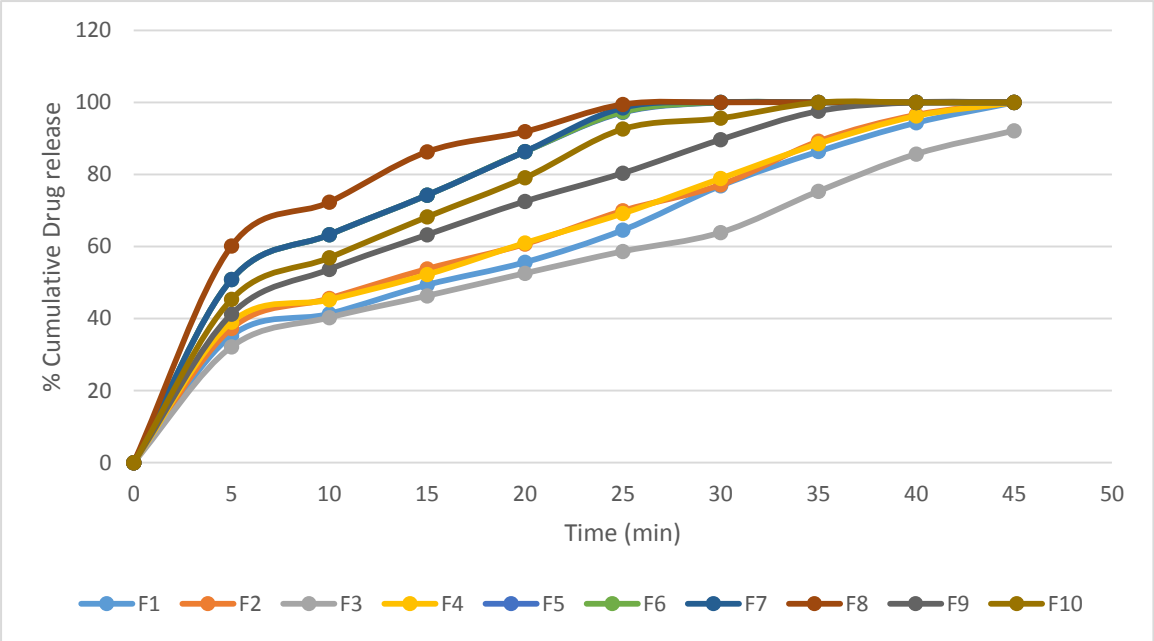

Figure 4: *In vitro* Drug Release Profile (F1-F5)

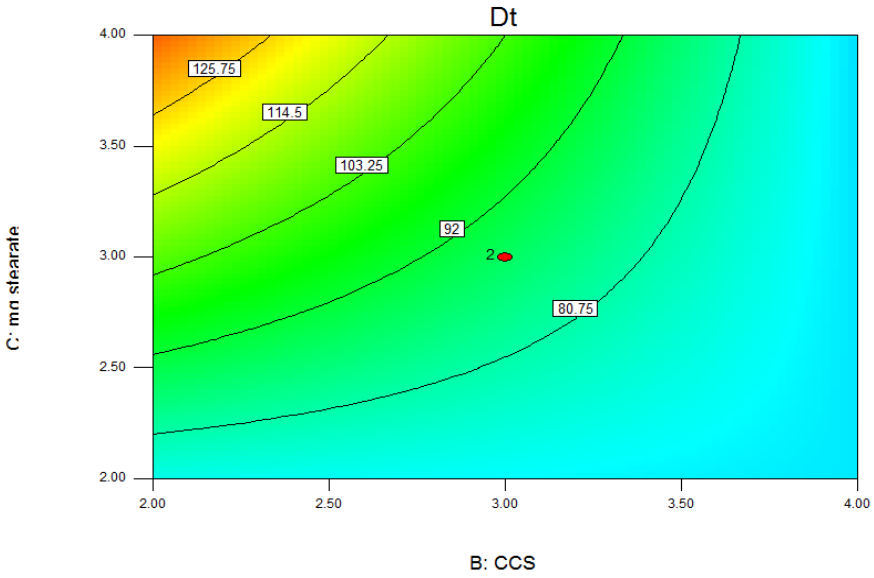

Figure 5: Contour plot showing the effect of amount of CCS and Magnesium stearate on Disintegration time.

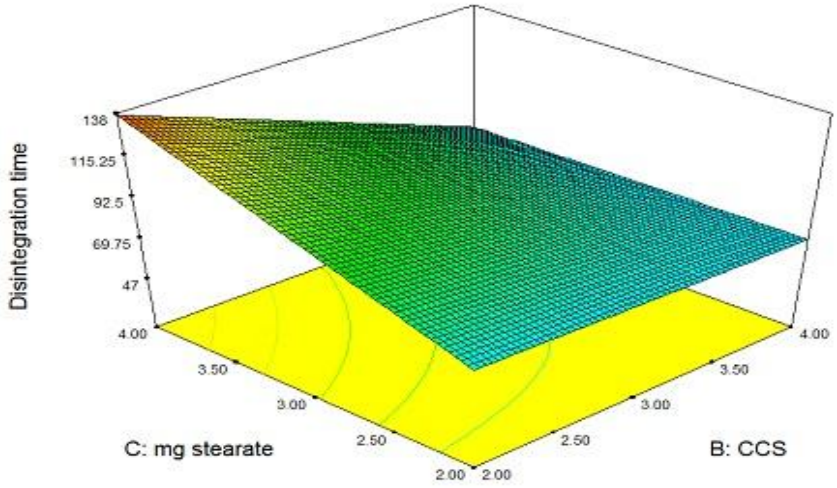

Figure 6: 3D Response Surface Plot Showing Effect of CCS and Magnesium stearate on Disintegration time

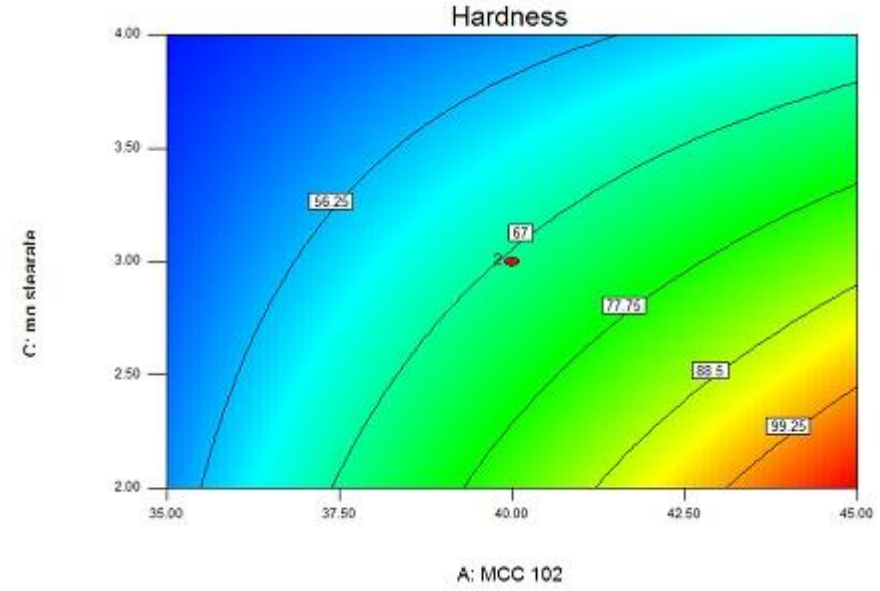

Figure 7: Contour plot showing the effect of amount of MCC and Magnesium stearate on Hardness

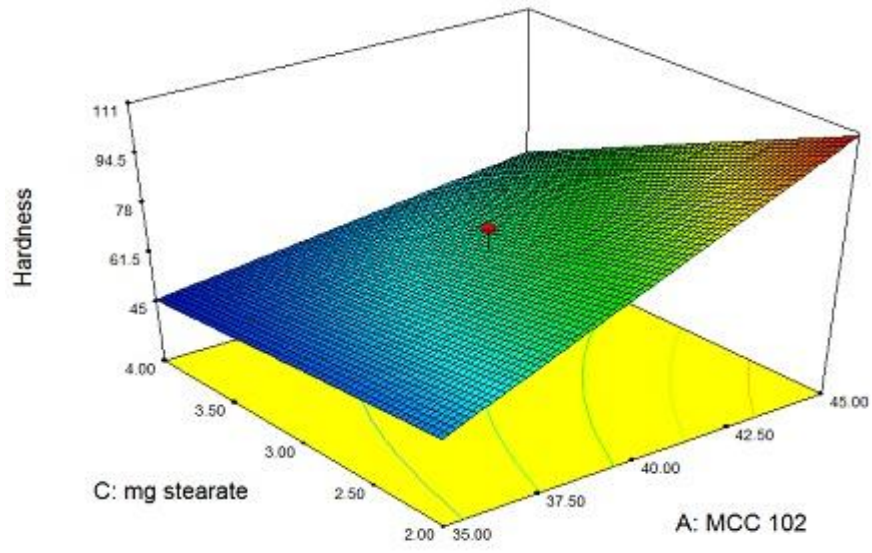

Fig. 8: 3D Response Surface Plot Showing Effect of MCC and Magnesium stearate on Hardness

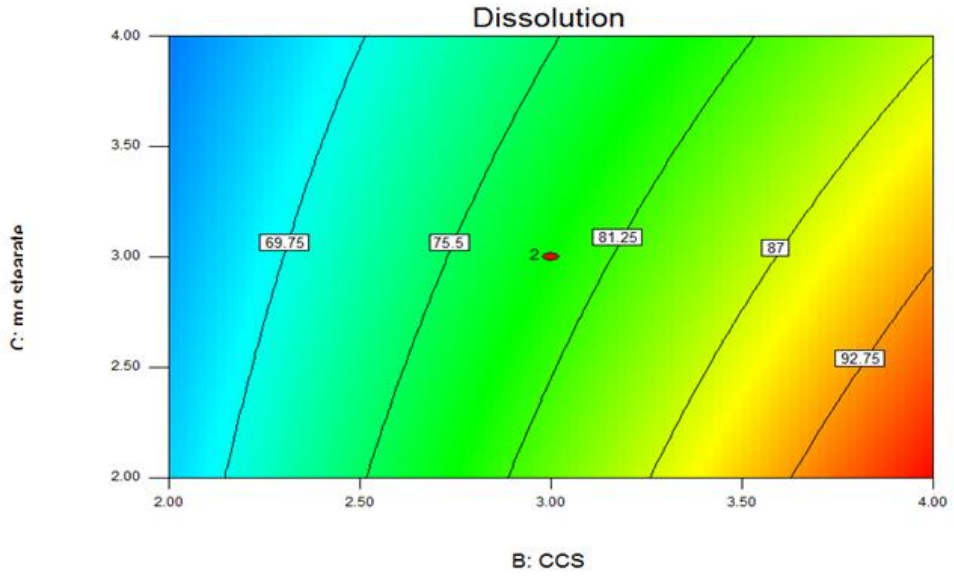

Figure 9: Contour plot showing the effect of amount of CCS and Magnesium stearate on Dissolution

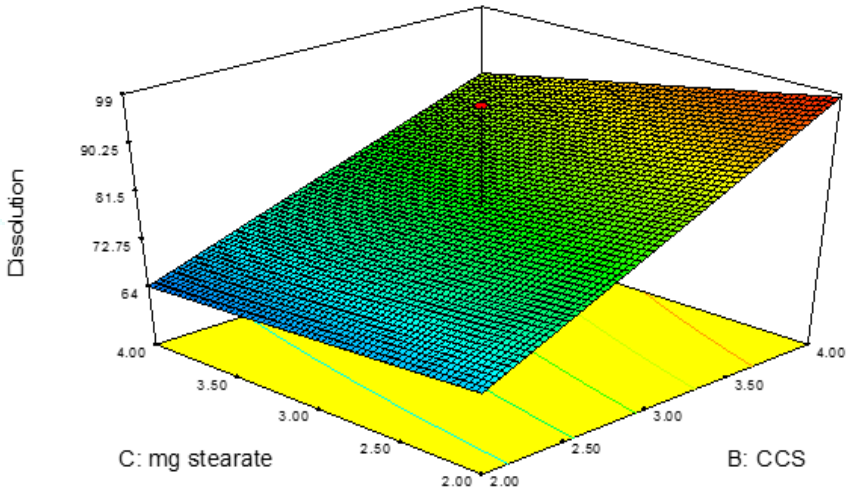

Fig Fig. 10: 3D Response Surface Plot Showing Effect of CCS and Magnesium stearate on Dissolution

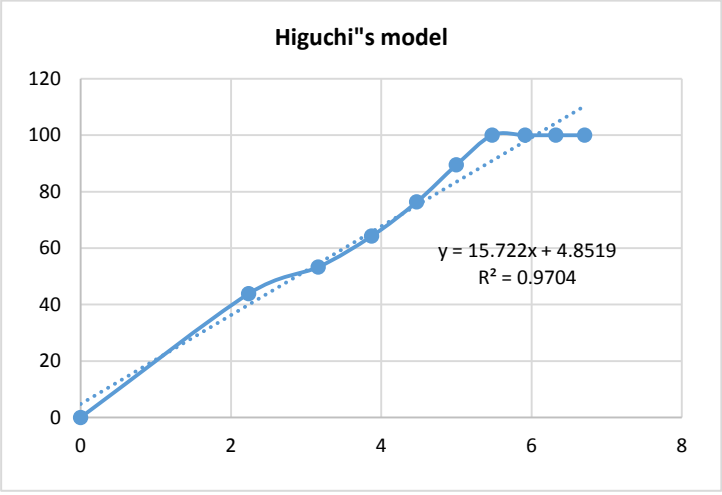

Figure 12: Release kinetic mechanism of optimized formulation O_1

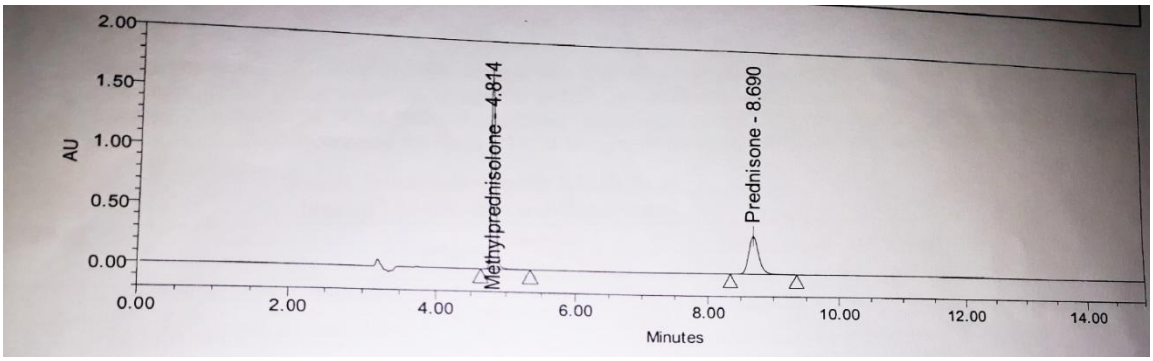

Fig. 13: Sample Graph of Methylprednisolone for assay

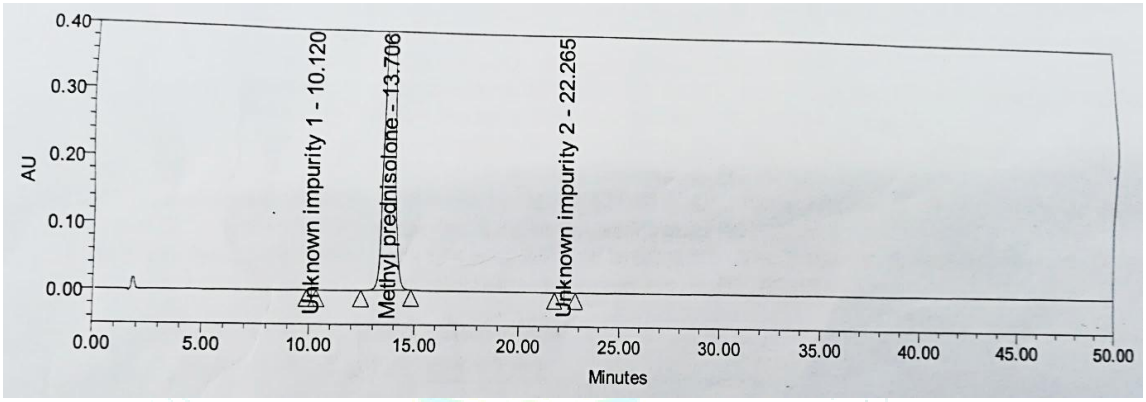

Fig. 14: Sample Graph of Methylprednisolone for Related substances

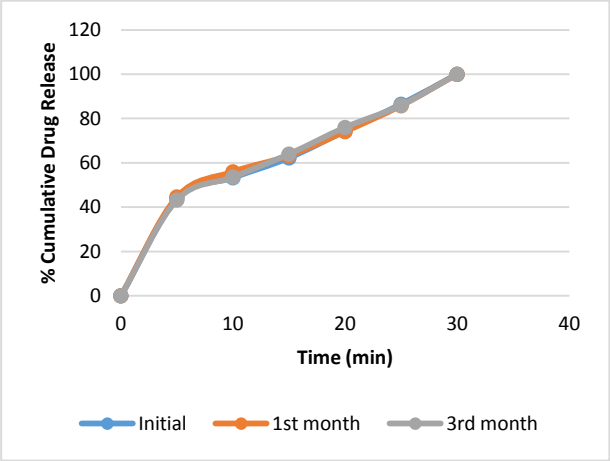

Figure 15: *In vitro* drug release study of optimized formulation before and after stability